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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,668	01/27/2004	David B. Rozema	25775 US1	9890

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
10/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,668	ROZEMA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7,8,12,16,17,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5,7,12 and 16* is/are allowed.

6)☒ Claim(s) *8,17,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/2009 has been entered.

Receipt is acknowledged of an amendment, filed 7/7/2009, in which claims 5 and 12 were amended. Claims 5, 7, 8, 12, 16, 17, 21 and 22 are pending and under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 5/3/2005, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Objections

Claims 8 and 21are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 8 and 21 indirectly depend from claim 5. Claim 5 is drawn to a method that consists of the steps of a) forming a styrene-maleic anhydride random copolymer; b) increasing hydrophobicity of the copolymer by randomly attaching hydrophobic groups along the copolymer backbone in a sufficient amount to form a membrane

active polyanion capable of lysing mammalian cell membranes at pH 6.5 wherein randomly attaching hydrophobic groups along the copolymer backbone consists of reacting hydrophobic amines or hydrophobic alcohols with the anhydride monomers in the copolymer; and c) contacting said cell with said polynucleotide and said membrane active polyanion such that the polynucleotide and the membrane active polyanion are endocytosed by the cell. Claims 8 and 21 further comprise the step of covalently linking a functional group to an anhydride monomer in the polymer. A step of covalently linking a functional group is not found in independent claim 5. In claim 5, the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948). Thus, it is not proper for claims 8 and 21 to require the covalent linkage of a functional group to an anhydride monomer in the polymer.

Claims 17 and 22 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 17 and 22 depend from claim 12. Claim 12 is drawn to a method that consists of the steps of a) forming a butyl vinyl ether-maleic anhydride alternating copolymer; b) increasing hydrophobicity of the copolymer by randomly attaching hydrophobic groups along the copolymer backbone in a sufficient amount to form a membrane active polyanion capable of lysing mammalian cell membranes at pH 6.5 wherein randomly attaching hydrophobic groups along the copolymer backbone consists of reacting hydrophobic amines or hydrophobic alcohols with anhydride monomers in the copolymer; and c) contacting said cell with said polynucleotide and said membrane active polyanion such that the

polynucleotide and the membrane active polyanion are endocytosed by the cell. Claims 17 and 22 further comprise the step of covalently linking a functional group to an anhydride monomer in the polymer. A step of covalently linking a functional group is not found in independent claim 12. In claim 12, the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948). Thus, it is not proper for claims 17 and 22 to require the covalent linkage of a functional group to an anhydride monomer in the polymer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 01/49841; see the entire reference) in view of Oda et al (Journal of the National Cancer Institute, Vol. 79, No. 6, pages 1205-1211, 1987, cited on the IDS filed 10/4/2004; see the entire reference). This is a new rejection.

Wolff teaches the synthesis of a polymer from monomers (e.g., page 4, line 25 to page 8, line 24). Wolff teaches that other groups can be attached to the polymer after its formation, including agents to disrupt endosomes (e.g., page 8, line 26 to page 9, line 13). Wolff teaches that polyanions effectively enhance the gene deliver/gene expression capabilities of all major

classes of polycation gene delivery reagents (e.g., page 16, lines 9-10). Wolff teaches that copolymers of polymaleic acid can be used to recharge DNA/polycation particles (e.g., page 16, lines 34-30). Wolff teaches that the polyanion may be covalently joined to the polycation using a variety of chemical reactions without the use of a crosslinker, and the polyanion can contain reactive groups that covalently attach to groups on the polycation (e.g., page 17, lines 16-17). Wolff teaches that the polyanion-polycation molecule is mixed with polynucleotide and delivered to a cell (e.g., page 12, lines 1-6; page 17, line 16 to page 19, line 15). Wolff exemplifies processes for delivering a polynucleotide to the cytoplasm of a cell in vitro consisting of (i) providing a formed polyanion polymer, (ii) covalently attaching IPEI, which is a functional membrane active compound, to the polyanion, (iii) contacting the cell in vitro with the IPEI-polyanion polymer and polynucleotide, such that the polynucleotide and IPEI-polyanion polymer are endocytosed by the cell (e.g., Examples).

Wolff does not teach the method where the polyanion is provided by forming a styrene-maleic anhydride random copolymer, and reacting hydrophobic amines or hydrophobic alcohols with anhydride monomers in the copolymer.

Oda et al teach a process consisting of a) forming a styrene-maleic anhydride random copolymer (SMA); b) reacting 50-70% (mol/mol) of the carboxyl groups of maleic acid with butyl alcohol to form a butyl ester derivative of SMA; c) conjugating the butyl ester SMA with the drug neocarzinostatin (NCS) to form SMANCS; and d) contacting a cell *in vitro* with the SMANCS such that the SMANCS is endocytosed by the cell (e.g., paragraph bridging pages 1205-1206page 1206, right column, last full paragraph; page 1209, right column, full paragraph; page 1210, paragraph bridging columns). Oda et al teach that compounds internalized into cells

by endocytosis are found in intracellular acidic vesicles before being fused with lysozomes, and an acidic environment may greatly affect the state of the carboxyl group of both NCS (total of 14 residues) and SMANCS (at least 28 residues) (e.g., page 1209, Discussion). Oda et al teach that, in the acidic environment, the carboxyl groups become more hydrophobic, thus favoring interaction with the lipid bilayer of the cell membrane, resulting in inversion of the carboxyl groups into the membrane and penetration of the drugs into the cytoplasm (e.g., page 1209, Discussion).

Both Wolff and Oda et al teach the use of polymers to deliver a molecule to the cytoplasm of a cell in vitro. Wolff teaches the use of copolymers of polymaleic acid in the method of delivering a polynucleotide, and Oda et al teach the use of butyl ester derivative of styrene maleic acid anhydride random copolymer (butyl SMA) for the delivery of a drug to a cell in vitro, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the butyl SMA of Oda et al for the polyanion of Wolff in order to achieve the predictable result of using butyl SMA to improve the delivery of a polynucleotide to a cell in vitro.

Claims 17 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 01/49841; see the entire reference) in view of Saettone et al. ("Inserts for Sustained Ocular Delivery of Pilocarpine: Evaluation of a Series of Partial Esters of (Maleic Acid – Alkyl Vinyl Ether) Alternating Copolymers." Polymers in Medicine III: Third International Conference on Polymers in Medicine, Porto Cervo Italy, Ed. Migliarese, C., et al. Elsevier Science Publishers B.V., pages 209-224, 1998; see the entire reference). This is a new rejection.

Wolff teaches the synthesis of a polymer from monomers (e.g., page 4, line 25 to page 8, line 24). Wolff teaches that other groups can be attached to the polymer after its formation, including agents to disrupt endosomes (e.g., page 8, line 26 to page 9, line 13). Wolff teaches that polyanions effectively enhance the gene deliver/gene expression capabilities of all major classes of polycation gene delivery reagents (e.g., page 16, lines 9-10). Wolff teaches that copolymers of polymaleic acid can be used to recharge DNA/polycation particles (e.g., page 16, lines 34-30). Wolff teaches that the polyanion may be covalently joined to the polycation using a variety of chemical reactions without the use of a crosslinker, and the polyanion can contain reactive groups that covalently attach to groups on the polycation (e.g., page 17, lines 16-17). Wolff teaches that the polyanion-polycation molecule is mixed with polynucleotide and delivered to a cell (e.g., page 12, lines 1-6; page 17, line 16 to page 19, line 15). Wolff exemplifies processes for delivering a polynucleotide to the cytoplasm of a cell in vitro consisting of (i) providing a formed polyanion polymer, (ii) covalently attaching IPEI, which is a functional membrane active compound, to the polyanion, (iii) contacting the cell in vitro with the IPEI-polyanion polymer and polynucleotide, such that the polynucleotide and IPEI-polyanion polymer are endocytosed by the cell (e.g., Examples).

Wolff does not teach the method where the polyanion is provided by forming a butyl vinyl ether maleic anhydride alternating copolymer, and reacting hydrophobic amines or hydrophobic alcohols with anhydride monomers in the copolymer.

Saettone et al teach the synthesis of butyl vinyl ether-maleic anhydride alternating copolymer, and the reaction of anhydride moieties of the copolymer with hydrophobic alcohol (e.g., page 221, section a2) Polymers; page 214Table 1). Saettone et al specifically teach the

methyl ester of butyl vinyl ether maleic anhydride (M-BVEMA), which was 40% esterified or 54% esterified (e.g., Table 1; page 214). Saettone et al teach contacting a cell with M-BVEMA and pilocarpine base (PiB, a drug) (e.g., pages 211-212, section b) preparation of the inserts). Saettone et al teach that 54% esterified M-VBEMA significantly increased delivery of the drug to cells (e.g., pages 218-220, section b3) Biological tests; Figure 4). Saettone et al teach that alkyl half esters of (maleic acid – alkyl vinyl ether) copolymers are attractive materials for drug delivery on account of their widespread acceptance in pharmaceutical preparations, and of the possibility of varying their structural characteristics by simple chemical modifications occurring at the level of the anhydride group (e.g., paragraph bridging pages 220-221).

Both Wolff and Saettone et al teach the use of polymers to deliver a molecule to the cytoplasm of a cell in vitro. Wolff teaches the use of copolymers of polymaleic acid in the method of delivering a polynucleotide, and Saettone et al teach the use of a methyl ester of butyl vinyl ether maleic anhydride alternating copolymer (M-BVEMA) for the delivery of a drug to a cell, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the M-BVEMA of Saettone et al for the polyanion of Wolff in order to achieve the predictable result of using M-BVEMA to improve the delivery of a polynucleotide to a cell in vitro.

Where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 U.S.C. 102, or "prima facie obviousness" under 35

U.S.C. 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the methyl ester of butyl vinyl ether maleic anhydride alternating copolymer of Sacttone et al is identical to the compound disclosed as M-BVEMA in the present specification. M-BVEMA is disclosed as having the ability to lyse mammalian cell membranes at pH 6.5 (e.g., Figure 3).

Response to Arguments - 35 USC § 103

The rejection of claims 5, 7, 8 and 21 under 35 U.S.C. 103(a) as being unpatentable over Adams et al in view of Heller et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/7/2009.

The rejection of claims 12, 16, 17 and 22 under 35 U.S.C. 103(a) as being unpatentable over Adams et al in view of Heller et al Tonge et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 7/7/2009.

With respect to the new rejections presented above, Applicant's arguments filed 7/7/2009 have been fully considered but they are not persuasive.

The response notes that in Takeda v. Alphapharm and Eisai Co. Ltd. v. Dr. Reddy's Laboratories, the courts have found that there must be motivation in the prior art to select a lead compound. Thus, the response asserts that there must be motivation to select a styrene-maleic anhydride random copolymer or butyl vinyl ether-maleic anhydride alternating copolymer. The response notes that the courts have found that a finite number of identified, predictable solutions

is critical to obviousness and turns on the evidence of available to a person of skill when the invention was made.

A suggestion or motivation to combine references is an appropriate method for determining obviousness; however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham. KSR*, 550 U.S. 398, 127 S. Ct. 1727, 82 *U.S.P.Q.*2d 1385. See MPEP § 2141 and § 2143. In the instant case, Wolff identifies copolymers of polymaleic acid as being suitable for use in the method. Oda et al specifically teach a butyl ester of styrene maleic anhydride random copolymer that necessarily meets the functional limitations of the claims, and Saettone et al teach a methyl ester of a butyl vinyl ether maleic anhydride alternating copolymer that necessarily meets the functional limitations of the claims. Wolff teaches the use of copolymers of polymaleic acid for delivery of a polynucleotide to the cytoplasm of a cell. Oda et al and Saettone et al teach the suitability of specific copolymers of polymaleic acid for drug delivery. Thus, the function of the particular copolymers in nucleic acid and drug delivery was known in the art, and it would have been obvious to one of ordinary skill in the art to substitute the specific copolymers taught by Oda et al and Saettone et al for the general copolymer of polymaleic acid taught by Wolff in order to achieve the predictable result of providing a specific copolymer of polymaleic acid covalently linked to IPEI to deliver a polynucleotide to the cytoplasm of a cell in vitro.

Conclusion

Claims 5, 7, 12 and 16 are allowed. The art of record does not teach or suggest the use of the claimed polymers to deliver a polynucleotide to the cytoplasm of a cell in the absence of a cationic transfection reagent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636